This Month in *The Journal*

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A Heated Debate over Hotspots

Johnston and Cutler, page 774
Recombination hotspots are defined as genomic areas that undergo higher rates of recombination than do their surrounding areas. But what, at a molecular level, defines these hotspots, and how prevalent are they in the human genome? Many investigators point to a key role for PRDM9 binding in dictating the location of hotspots. Taking an alternative view, Johnston and Cutler examine the idea that human demographic history has distorted most analyses of hotspots. Whereas most models assume a constant effective population size over time, the authors posit that because older regions of the genome have undergone a greater number of total recombination events, they might appear to experience a higher rate of recombination. To address this possibility, they generated a model wherein recombination rates are constant but population sizes change. Their analysis shows that population bottlenecks alone can create the appearance of hotspots. Although the debate is far from over, this report should prompt researchers to more carefully analyze claims of hotspot discoveries.

A Genetic Brain Booster?

Ameur et al., page 809
Long-chain polyunsaturated fatty acids (LC-PUFAs) are essential for brain function. Although LC-PUFAs can be obtained from food, they are also synthesized from precursor molecules. Recent research has identified the enzymes—FADS1 and FADS2—that direct this synthesis, and interestingly, the genes that encode these proteins are positioned in a head-to-head orientation on chromosome 11. Therefore, it is possible that common regulatory mechanisms might be at play. In this issue, Ameur et al. take this idea further and show that two common haplotypes are associated with LC-PUFA biosynthesis. Strikingly, the haplotype associated with more efficient biosynthesis shows a signature of having undergone positive selection. Given the importance of LC-PUFAs for the brain, the authors postulate that this haplotype might have been beneficial for early humans in terms of promoting brain-size expansion, especially during periods in which fatty acids were scarce. This potential benefit, however, might now be detrimental: More rapid fatty-acid metabolism in the setting of a Western diet presents the risk of numerous health issues, including coronary heart disease. Might apparent ethnic differences in so-called lifestyle diseases be attributable to different haplotypes? The authors suggest that this might indeed be the case; genotyping to determine one's FADS haplotype could therefore be helpful in generating dietary recommendations.

NO to the Rescue

Nagamani et al., page 836
Argininosuccinic aciduria (ASA), an inborn error of metabolism, results from the lack of a key metabolic enzyme, argininosuccinate lyase (ASL). ASL is the only enzyme that can generate L-arginine, a precursor required for the proper function of several metabolic pathways. Affected individuals display hyperammonemia as well as several other defects, e.g., neurocognitive deficits and hypertension. Notably, although the standard treatment of L-arginine supplementation can prevent the hyperammonemia, longer-term defects, including hypertension, persist. In this issue, Nagamani et al. reason that supplementation with NO, a critical metabolite whose production relies on ASL function, might help to correct these "secondary" defects. Indeed, this treatment regimen was able to reverse a severe case of hypertension in an individual harboring compound heterozygous mutations in *ASL*. Moreover, the authors' findings also suggest that NO can improve neurocognitive function. Although this is a preliminary study of one individual, the marked improvement that was observed, in conjunction with the authors' gene-therapy studies in mice, suggests that NO supplementation has great promise in treating ASA. Indeed, this study provides a compelling example of what the future of personalized medicine might hold in store.

More Clues in the ASD Mystery

Sato et al., page 879
Autism spectrum disorder (ASD) is in the news a lot these days. Earlier this month, the US Centers for Disease Control reported that an estimated 1 in 88 children is

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affected. Although we now have a better handle on diagnosing ASD, the causes remain as elusive as ever. Many studies have pointed to potential roles for environmental factors, and there is much evidence to support a causative role of de novo mutations. However, it is clear that inherited mutations are also involved. In this issue, Sato et al. identify mutations—both inherited and de novo—that result in the deletion of *SHANK1* in individuals with ASD. Interestingly, these mutations appear to have reduced penetrance in females, perhaps providing some clues about the well-described male gender bias. *SHANK1* joins its family members, *SHANK2* and *SHANK3*, all of which encode neuronal scaffolding proteins, as being implicated in ASD etiology. Future experiments should help to uncover the exact role played by these proteins in the brain, perhaps shedding some light on why their absence can lead to ASD. Also, the authors identify additional mutations that, in conjunction with *SHANK1* deletions, probably contribute to their ASD phenotypes. The way in which interplay between mutations, along with gene-environment interactions, influences ASD is poorly understood, and much more research on this topic is needed. Indeed, although many pieces of the puzzle have been revealed, how they all fit together is still far from clear.

Ice Age Hiding Places

Pala et al., page 915

Throughout their history, human populations have faced numerous external stressors that caused population contractions. During such periods, humans are thought to have formed small groups in isolated geographic locations, or refugia. Once conditions improve, population expansions ensue, and movement out of the refugia into new territories follows. During the last ice age, humans sought refuge throughout Europe and the Near East (an area roughly equivalent to the present-day Middle East), but there is a lack of certainty regarding the dispersal patterns during the Late Glacial period. In this issue, Pala et al. analyze hundreds of new mtDNA sequences to show that humans moved from the Near East into Europe at this time. Prior to this report, most models posited that such movement did not occur until ~10,000 years later. However, these new findings suggest that such models should be re-examined because the previously detected signatures of Neolithic expansion might instead represent indigenous European dispersals. Although we will never know exactly what paths our ancestors took, findings such as this one help to paint a much clearer picture.